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(54) **Use of rapamycin in the manufacture of a medicament for preventing and heating hyperproliferactive vascular diseases, eventually in combination with mycophenolic acid**

(57)   This invention provides a method of preventing hyperproliferative vascular disease in a mammal by administering an antiproliferative effective amount of rapamycin alone or in combination with mycophenolic acid.

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Description

This invention relates to a method of preventing hyperproliferative vascular disease, in particular to a new use of rapamycin.

Many individuals suffer from heart disease caused by a partial blockage of the blood vessels that supply the heart with nutrients. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Typically vascular occlusion is preceded by vascular stenosis resulting from intimal smooth muscle cell hyperplasia. The underlying cause of the intimal smooth muscle cell hyperplasia is vascular smooth muscle injury and disruption of the integrity of the endothelial lining. The overall disease process can be termed a hyperproliferative vascular disease because of the etiology of the disease process. Intimal thickening following arterial injury can be divided into three sequential steps: 1) initiation of smooth muscle cell proliferation following vascular injury, 2) smooth muscle cell migration to the intima, and 3) further proliferation of smooth muscle cells in the intima with deposition of matrix. Investigations of the pathogenesis of intimal thickening have shown that, following arterial injury, platelets, endothelial cells, macrophages and smooth muscle cells release paracrine and autocrine growth factors (such as platelet derived growth factor, epidermal growth factor, insulin-like growth factor, and transforming growth factor) and cytokines that result in the smooth muscle cell proliferation and migration. T-cells and macrophages also migrate into the neointima. [Haudenschild, C., Lab. Invest. 41: 407 (1979); Clowes, A., Circ. Res. 56: 139 (1985); Clowes, A., J, Cardiovas. Pharm. 14 (Suppl. 6): S12 (1989); Manderson, J., Arterio. 9: 289 (1989); Forrester, J., J. Am. Coll. Cardiol. 17: 758 (1991)]. This cascade of events is not limited to arterial injury, but also occurs following injury to veins and arterioles.

Vascular injury causing intimal thickening can be broadly categorized as being either biologically or mechanically induced. Artherosclerosis is one of the most commonly occurring forms of biologically mediated vascular injury leading to stenosis. The migration and proliferation of vascular smooth muscle plays a crucial role in the pathogenisis of artherosclerosis. Artherosclerotic lesions include massive accumulation of lipid laden "foam cells" derived from monocyte/macrophage and smooth muscle cells. Formation of "foam cell" regions is associated with a breech of endothelial integrity and basal lamina destruction. Triggered by these events, restenosis is produced by a rapid and selective proliferation of vascular smooth muscle cells with increased new basal lamina (extracellular matrix) formation and results in eventual blocking of arterial pathways. [Davies, P.F., Artherosclerosis Lab. Invest. 55: 5 (1986)].

Mechanical injuries leading to intimal thickening result following balloon angioplasty, vascular surgery, transplantation surgery, and other similar invasive processes that disrupt vascular integrity. Intimal thickening following balloon catheter injury has been studied in animals as a model for arterial restenosis that occurs in human patients following balloon angioplasty. Clowes, Ferns, Reidy and others have shown that deendothelilization with an intraarterial catheter that dilates an artery injures the innermost layers of medial smooth muscle and may even kill some of the innermost cells. [Schwartz, S.M., Human Pathology 18: 240 (1987); Fingerle, J., Ateriosclerosis 10: 1082 (1990)] Injury is followed by a proliferation of the medial smooth muscle cells, after which many of them migrate into the intima through fenestrae in the internal elastic lamina and proliferate to form a neointimal lesion.

Vascular stenosis can be detected and evaluated using angiographic or sonographic imaging techniques [Evans, R.G., JAMA 265: 2382 (1991)] and is often treated by percutaneous transluminal coronary angioplasty (balloon catheterization). Within a few months following angioplasty, however, the blood flow is reduced in approximately 30-40 percent of these patients as a result of restenosis caused by a response to mechanical vascular injury suffered during the angioplasty procedure, as described above. [Pepine, C., Circulation 81: 1753 (1990); Hardoff, R., J. Am. Coll. Cardiol. 15 1486 (1990)].

In an attempt to prevent restenosis or reduce intimal smooth muscle cell proliferation following angioplasty, numerous pharmaceutical agents have been employed clinically, concurrent with or following angioplasty. Most pharmaceutical agents employed in an attempt to prevent or reduce the extent of restenosis have been unsuccessful. The following list identifies several of the agents for which favorable clinical results have been reported: lovastatin [Sahni, R., Circulation 80 (Suppl.) 65 (1989); Gellman, J., J. Am. Coll. Cardiol. 17: 251 (1991)]; thromboxane A_2 synthetase inhibitors such as DP-1904 [Yabe, Y., Circulation 80 (Suppl.) 260 (1989)]; eicosapentanoic acid [Nye, E., Aust. N.Z. J. Med. 20: 549 (1990)]; ciprostene (a prostacyclin analog) [Demke, D., Brit. J. Haematol 76 (Suppl.): 20 (1990); Darius, H., Eur. Heart J. 12 (Suppl.): 26 (1991)]; trapidil (a platelet derived growth factor) [Okamoto, S., Circulation 82 (Suppl.): 428 (1990)]; angiotensin converting enzyme inhibitors [Gottlieb, N., J. Am. Coll. Cardiol. 17 (Suppl. A): 181A (1991)]; and low molecular weight heparin [de Vries, C., Eur. Heart J. 12 (Suppl.): 386 (1991)].

In an attempt to develop better agents for preventing or reducing smooth muscle proliferation and intimal thickening, the use of balloon catheter induced arterial injury in a variety of mammals has been developed as a standard model of vascular injury that will lead to intimal thickening and eventual vascular narrowing. [Chevru, A., Surg. Gynecol. Obstet. 171: 443 (1990); Fishman, J., Lab. Invest. 32: 339 (1975); Haudenschild, C., Lab. Invest. 41: 407 (1979); Clowes, A.W., Lab. Invest. 49: 208 (1983); Clowes, A.W., J. Cardiovas. Pharm. 14: S12 (1989); and Ferns, G.A., Science 253: 1129 (1991)]. Many compounds have been evaluated in this standard animal model. The immunosuppressive agent cy-

closporin A has been evaluated and has produced conflicting results. Jonasson reported that cyclosporin A caused an inhibition of the intimal proliferative lesion following arterial balloon catheterization in vivo, but did not inhibit smooth muscle cell proliferation in vitro. [Jonasson, L., Proc. Natl. Acad. Sci. 85: 2303 (1988)]. Ferns, however reported that when deendothelilized rabbits were treated with cyclosporin A, no significant reduction of intimal proliferation was observed in vivo. Additionally, intimal accumulations of foamy macrophages, together with a number of vacuolated smooth muscle cells in the region adjacent to the internal elastic lamina were observed, indicating that cyclosporin A may modify and enhance lesions that form at the sites of arterial injury. [Ferns, G.A., Circulation 80 (Supp): 184 (1989); Ferns, G., Am. J. Path. 137: 403 (1990)].

Rapamycin, a macrocyclic triene antibiotic produced by Streptomyces hygroscopicus [U.S. Patent 3,929,992] has been shown to prevent the formation of humoral (IgE-like) antibodies in response to an albumin allergic challenge [Martel, R., Can. J. Physiol. Pharm. 55: 48 (1977)], inhibit murine T-cell activation [Staruch, M., FASEB 3: 3411 (1989)], prolong survival time of organ grafts in histoincompatible rodents [Morris, R., Med. Sci. Res. 17: 877 (1989)], and inhibit transplantation rejection in mammals [Calne, R., European Patent Application 401,747]. Rapamycin blocks calcium-dependent, calcium-independent, cytokine-independent and constitutive T and B cell division at the G1-S interface. Rapamycin inhibits gamma-interferon production induced by II-1 and also inhibits the gamma-interferon induced expression of membrane antigen. [Morris, R.E., Transplantation Rev. 6: 39 (1992)]. The use of rapamycin in preventing coronary graft atherosclerosis (CGA) in rats has been disclosed by Meiser [J. Heart Lung Transplant 9: 55 (1990)]. Arterial thickening following transplantation, known as CGA, is a limiting factor in graft survival that is caused by a chronic immunological response to the transplanted blood vessels by the transplant recipient's immune system. [Dec. G, Transplantation Proc. 23: 2095 (1991) and Dunn, M. Lancet 339: 1566 (1992)]. The disclosed invention is distinct from the use of rapamycin for preventing CGA, in that CGA does not involve injury to the recipients own blood vessels; it is a rejection type response. The disclosed invention is related to vascular injury to native blood vessels. The resulting intimal smooth muscle cell proliferation dose not involve the immune system, but is growth factor mediated. For example, arterial intimal thickening after balloon catheter injury is believed to be caused by growth factor (PGDF, bFGF, TGFb, IL-1 and others)-induced smooth muscle cell proliferation and migration. [Ip, J.H., J. Am. Coll. Cardiol 15: 1667 (1990)]. Ferns has also shown that the immune response is not involved in arterial intimal thickening following balloon catheterization, as he found that there was no difference in intimal thickening between arteries from athymic nude rats (rats lacking T-cells) and normal rats after balloon catheterization [Am. J. Pathol. 138: 1045 (1991)].

This invention provides a method of preventing or treating hyperproliferative vascular disease in a mammal in need thereof by administering an antiproliferative effective amount of rapamycin to said mammal wherein said administration is initiated prior to the occurrence of said vascular disease. Preferably the rapamycin is administered orally, parenterally, intravascularly, intranasally, intrabronchially, transdermally, rectally, or via a vascular stent impregnated with rapamycin.

This invention also provides use of rapamycin in the preparation of a medicament for administration to a mammal for a sufficient period before and if necessary after the mammal incurs a mechanically mediated vascular injury to substantially prevent intimal smooth muscle cell proliferation, restenosis and/or vascular occlusion occurring following the vascular injury.

As such, rapamycin is useful in preventing intimal smooth muscle cell hyperplasia, restenosis, and vascular occlusion in a mammal, following mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Mechanically mediated vascular injury includes, but is not limited to vascular injury caused by catheterization procedures or vascular scraping procedures such as percutaneous transluminal coronary angioplasty; vascular surgery; transplantation surgery; laser treatment; and other invasive procedures which disrupt the integrity of the vascular intima or endothelium. In particular, rapamycin is particularly useful for the prevention of restenosis following a percutaneous transluminal coronary angioplasty procedure.

Preventing includes inhibiting the development of and prophylactically preventing hyperproliferative vascular disease in a susceptible mammal.

This invention also provides a method of using a combination of rapamycin and mycophenolic acid for the same utilities described above. Mycophenolic acid, an antiproliferative antimetabolite, inhibits inosine monophosphate dehydrogenase and guanosine monophosphate synthetase, enzymes in the de novo purine biosynthetic pathway. This results in an inhibition of DNA synthesis which causes an accumulation of cells at the G1-S interface. Other combinations containing rapamycin that are useful for preventing or treating hyperproliferative vascular disease will be apparent to one skilled in the art. These include, but are not limited to, using rapamycin in combination with other antiproliferative antimetabolites.

The effect of rapamycin on hyperproliferative vascular disease was established in an in vivo standard pharmacological test procedure that emulates the hyperproliferative effects observed in mammals that are undergoing intimal smooth muscle proliferation and are therefore developing restenosis. The combination of rapamycin and mycophenolic acid was evaluated in the in vivo test procedure. The procedure and the results obtained are described below.

Rapamycin, and rapamycin plus mycophenolic acid, were evaluated in an in vivo standard pharmacological test procedure that emulates the vascular injury suffered and restenosis that develops following percutaneous transluminal

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coronary angioplasty in humans. The ability of a test compound to inhibit restenosis was determined by comparing intimal thickening in mammals treated with test compound following balloon catheterization versus intimal thickening in untreated control mammals after the same test procedure. [Chevru, A., Surg. Gvnecol. Obstet. 171: 443 (1990); Fishman, J., Lab. Invest. 32: 339 (1975); Haudenschild, C., Lab. Invest. 41: 407 (1979); Clowes, A.W., Lab. Invest. 49: 208 (1983); Clowes, A.W., J. Cardiovas. Pharm. 14: S12 (1989); and Ferns, G.A., Science 253: 1129 (1991)]. The following briefly describes the procedure that was used. Rats were divided into treatment groups, as shown in the tables below, and one control group. The treatment groups received either rapamycin or rapamycin plus mycophenolic acid beginning at 3 days before balloon catheterization (day -3). On day 0, the left carotid arteries of male Sprague-Dawley rats were injured with an inflated 2Fr balloon catheter. During a 13 day postoperative period, the treated rats continued daily treatment. Treatment was therefore administered from 3 days preoperatively to until 13 days postoperatively. One untreated group was used as an injured control to establish the amount of intimal growth in the absence of treatment. The rats in these groups underwent balloon catheterization as described above on day 0, but received no drug treatment either pre- or post-operatively. The right carotid was used as an uninjured control in all groups. After the 14-day period, the rats were sacrificed, and the carotids removed. The mean areas of the intima and blood vessel wall were measured by morphometry. Results are expressed as an intima percent which can be expressed according to the following formula:

$$\frac{\text{area of intima}}{\text{area of vessel}} * 100$$

The following table shows the results that were obtained.

EFFECT OF RAPAMYCIN ON INTIMAL THICKENING IN INJURED CAROTID ARTERIES (DAY 14)

Group	Dose	Treatment Days	Intima Percent ± S.E.
Uninjured Control			0.00 ± 0.00
Untreated Injured Control			44.51 ± 5.03
Rapamycin	1.5 mg/kg	-3 - 13*	9.85 ± 1.15
Rapamycin	1.5 mg/kg	-3 - 3	30.7 ± 6.67
Rapamycin	1.5 mg/kg	-3 - 0	37.31 ± 4.33
Rapamycin	1.5 mg/kg	3 - 13	44.38 ± 5.49

*Treatment from three days pre-balloon catheterization to day 13 days post-catheterization.

The results in the table above show that rapamycin prevented the development of restenosis following a balloon angioplasty procedure of the carotid artery, when rapamycin was administered from three days pre-angioplasty until day 13. Treatment from day minus 3 until day 3 or day 0 afforded a lesser degree of prevention, and treatment from day 3 to day 13 did not prevent restenosis.

In a modified test procedure, treatment with rapamycin or rapamycin plus mycophenolic acid were stopped on day 14, as above, but the animals were not sacrificed immediately. The table below shows the results obtained where rats underwent a balloon catheterization procedure of the carotid artery on day 0, and were sacrificed and examined morphometrically on day 44. The treatment regimen is described in the table.

EFFECT OF RAPAMYCIN + MPA ON INTIMAL THICKENING IN INJURED CAROTID ARTERIES (DAY 44)			
Group	Dose	Treatment Days	Intima Percent ± S.E.
Uninjured Control			0.00 ± 0.00
Untreated Injured Control			62.85 ± 3.63
Rapamycin + MPA	40/1.5 mg/kg	0-13	50.39 ± 2.58
Rapamycin + MPA	40/1.5 mg/kg	0-30	53.55 ± 2.85
Rapamycin + MPA	40/1.5 mg/kg	-3 - 13	18.76 ± 10.6

These results show that treatment with rapamycin and mycophenolic acid from day minus 3 to day 13 did effectively prevent restenosis at day 44, whereas the regimens which did not include drug administration before the angioplasty procedure did not effectively prevent restenosis at day 44.

Similar results were obtained when rat thoracic aortas were subjected to a balloon catheterization procedure, as

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described above, on day 0. The rats were either sacrificed and examined on day 14 or on day 44. The results obtained with rapamycin and rapamycin plus mycophenolic acid (MPA) are shown in the table below.

EFFECT OF RAPAMYCIN AND RAPAMYCIN + MPA ON INTIMAL THICKENING IN INJURED THORACIC AORTAS			
Day 14 results			
Group	Dose	Treatment Days	Intima Percent ± S.E.
Uninjured Control Untreated Injured Control Rapamycin + MPA	40/1.5 mg/kg	-3 -13	0.00 ± 0.00 15.52 ± 2.99 0.00 ± 0.00
Day 44 Results			
Group	Dose	Treatment Days	Intima Percent ± S.E.
Uninjured Control Untreated Injured Control Rapamycin Rapamycin + MPA	1.5 mg/kg 40/1.5 mg/kg	-3 -13 -3 -13	0.00 ± 0.00 28.76 ± 6.52 0.00 ± 0.00 8.76 ± 3.34

The results in the table above show that treatment with rapamycin from 3 days preoperatively until 13 days postoperatively completely prevented the development of restenosis 44 days after a balloon catheterization of the thoracic aorta. Using the same treatment regimen, rapamycin plus mycophenolic acid completely prevented restenosis 14 days after balloon catheterization and significantly prevented restenosis 44 days following balloon catheterization.

Similarly, day minus 3 to day 13 treatment with rapamycin plus mycophenolic acid completely prevented restenosis 14 days after balloon catheterizaton of the abdominal aortas in rats. These results are shown in the table below.

EFFECT OF RAPAMYCIN + MPA ON INTIMAL THICKENING IN INJURED ABDOMINAL AORTAS (DAY 14)			
Group	Dose	Treatment Days	Intima Percent ± S.E.
Uninjured Control Untreated Injured Control Rapamycin + MPA	40/1.5 mg/kg	-3 -13	0.00 ± 0.00 10.17 ± 2.42 0.00 ± 0.00

The results in the tables above show that rapamycin, alone or in combination with mycophenolic acid, is useful in preventing restenosis following invasive procedures that disrupt the vascular endothelial lining, such as percutaneous transluminal coronary angioplasty, vascular catheterization, vascular scraping, vascular surgery, or laser treatment procedures. These data also show that the administration of rapamycin, alone or in combination with mycophenolic acid, from 3 days pre-catheterization to 13 days post-catheterization, allowed the endothelium to heal, while preventing intimal smooth muscle cell proliferation. That intimal proliferation did not occur 31 days after administration with rapamycin, alone or in combination with mycophenolic acid, had been stopped, demonstrates that the endothelial layer had regenerated, as intimal proliferation stops after the reestablishment of the endothelial layer. The reestablishment of an intact endothelial layer was confirmed by microscopic examination of the previously catheterized arteries after removal at 44 days.

From the data above, it is particularly preferred that treatment begin with rapamycin or rapamycin plus mycophenolic acid before the procedure is performed, and that treatment should continue after the procedure has been performed. The length of treatment necessary to prevent restenosis will vary from patient to patient. For percutaneous transluminal angioplasty procedures, it is preferred that treatment be administered from 3 or more days before the procedure and continuing for 8 or more days after the procedure. It is more preferred that administration will be for 3 or more days before the angioplasty procedure and continuing for 13 or more days after the procedure. The same administration protocol is applicable when rapamycin, alone or in combination with mycophenolic acid, is used to prevent restenosis following vascular catheterization, vascular scraping, vascular surgery, or laser treatment procedures.

The results of the <u>in vivo</u> standard test procedure demonstrates that rapamycin and rapamycin in combination with mycophenolic acid are useful in preventing hyperproliferative vascular disease.

As such, rapamycin and rapamycin in combination with mycophenolic acid are useful in treating intimal smooth muscle cell hyperplasia, restenosis, and vascular occlusion in a mammal, following mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Mechanically mediated

vascular injury includes, but is not limited to vascular injury caused by catheterization procedures or vascular scraping procedures such as percutaneous transluminal coronary angioplasty; vascular surgery; transplantation surgery; laser treatment; and other invasive procedures which disrupt the integrity of the vascular intima or endothelium.

When rapamycin is employed alone or in combination with mycophenolic acid in the prevention of hyperproliferative vascular disease, it can be formulated neat or with a pharmaceutical carrier to a mammal in need thereof. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compound can also be administered orally either in liquid or solid composition form.

Rapamycin, alone or in combination with mycophenolic acid, may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. Rapamycin, alone or in combination with mycophenolic acid, may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermiable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Rapamycin, alone or in combination with mycophenolic acid can be administered intravascularly or via a vascular stent impregnated with rapamycin, alone or in combination with mycophenolic acid, during balloon catheterization to provide localized effects immediately following injury.

Rapamycin, alone or in combination with mycophenolic acid, may be administered topically as a solution, cream, or lotion by formulation with pharmaceutically acceptable vehicles containing 0.1 - 5 percent, preferably 2%, of active compound.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedure, projected daily intravenous dosages of rapamycin, when administered as the sole active compound or in combination with mycophenolic acid, would be 0.001 - 25 mg/kg, preferably between 0.005 - 10 mg/kg, and more preferably between 0.01 - 5 mg/kg. Projected daily oral dosages of rapamycin, when administered as the sole active compound or in combination with mycophenolic acid, would be 0.005 - 50 mg/kg, preferably between 0.01 - 25 mg/kg, and more preferably between 0.05 - 10 mg/kg. Projected daily intravenous dosages of mycophenolic acid, when used in combination with rapamycin, would be 0.5 - 75 mg/kg and preferably between 5 - 50 mg/kg. Projected daily oral dosages of mycophenolic acid, when used in combination with rapamycin, would be 1 - 75 mg/kg and preferably between 10 - 50 mg/kg.

Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral,

intravascular, intranasal, intrabronchial, transdermal, or rectal administration will be determined by the administering physician based on experience with the individual subject treated. In general, rapamycin is most desirably administered at a concentration that will generally afford effective results without causing any harmful or deleterious side effects, and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

Claims

1 Use of rapamycin in the preparation of a medicament for administration to a mammal for a sufficient period before and after the mammal incurs a mechanically mediated vascular injury to substantially prevent intimal smooth muscle cell proliferation, restenosis and/or vascular occlusion occurring following the vascular injury.

2. Use of rapamycin in the preparation of a medicament for preventing intimal smooth muscle cell proliferation, restenosis and/or vascular occlusion following a mechanically mediated vascular injury to a mammal, said medicament being adapted to be administered for a sufficient time before and after the mammal incurs the vascular injury.

3. Use of rapamycin in the preparation of a medicament for preventing a hyperproliferative vascular disease selected from intimal smooth muscle cell proliferation, restenosis, and vascular occlusion following a mechanically mediated vascular injury to a mammal, wherein the medicament is administered for a sufficient time before and after the mammal incurs the vascular injury.

4. A use according to any one of claims 1 to 3 in which the medicament is to be administered for at least 10 days prior to the vascular injury.

5. A use according to any one of claims 1 to 4 in which the medicament is to be administered for at least 3 days prior to the vascular injury.

6. A use according to any one of claims 1 to 5 in which the medicament is to be administered daily preceding the vascular injury.

7. A use according to any one of claims 1 to 6 in which the medicament is to be administered for at least 5 days after the vascular injury.

8. A use according to any one of claims 1 to 7 in which the medicament is to be administered for at least 13 days after the vascular injury.

9 A use according to any one of claims 1 to 8 in which the medicament is adapted for administration to said mammal orally, parenterally, intravascularly, intranasally, intrabronchially, transdermally, rectally, or via a vascular stent impregnated with rapamycin.

10 A use according to any one of claims 1 to 9 wherein the mechanically mediated vascular injury is caused by vascular catheterization, vascular scraping, percutaneous transluminal coronary angioplasty, vascular surgery or laser treatment.

11. A use according to any one of claims 1 to 10 in which the medicament comprises an antiproliferative effective amount of a combination of rapamycin and mycophenolic acid.

12 A use according to any one of claims 1 to 11 wherein the mechanically mediated vascular injury is caused by vascular catheterization, vascular scraping, percutaneous transluminal coronary angioplasty, vascular surgery, or laser treatment.

13 A use according to any one of claims 1 to 12 preventing restenosis in a mammal resulting from said mammal undergoing a percutaneous transluminal coronary angioplasty procedure

14. A method of preventing restenosis in a mammal resulting from said mammal undergoing a percutaneous transluminal coronary angioplasty procedure which comprises administering an antirestenosis effective amount of rapamycin to said mammal orally, parenterally intravascularly, intranasally, intrabronchially, transdermally, rectally,

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or via a vascular stent impregnated with rapamycin, wherein the administration of rapamycin is initiated before the mammal undergoes the percutaneous transluminal coronary angioplasty procedure.

15. A method according to claim 14, wherein the rapamycin is administered for 3 or more days before the mammal undergoes the percutaneous transluminal coronary angioplasty procedure and said administration continues for 8 or more days following the percutaneous transluminal coronary angioplasty procedure.

16. A method according to claim 15, wherein the rapamycin is administered for at least 13 days following the percutaneous transluminal coronary angioplasty procedure.

17. A method according to any one of claims 14 to 16 which comprises administering rapamycin in combination with mycophenolic acid.

European Patent Office	EUROPEAN SEARCH REPORT	Application Number EP 95 30 3150

DOCUMENTS CONSIDERED TO BE RELEVANT

	Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
5	X	EP-A-0 551 182 (AMERICAN HOME PROD CORP) 14 July 1993 * claims; p.3, 1.24-52; p.5, 1.35 *	1-3, 6-14,17	A61K31/71 A61K31/365 A61K31/395 A61K31/66
	Y	* the whole document *	4,5,15, 16	
12	P,Y	CIRCULATION, vol. 90, no. 4, October 1994 page I306 MARX ET AL 'rapamycin inhibits phosphorylation of retinsoblastoma protein and blocks vascular smooth muscle cell proliferation' * the whole document *	4,5,15, 16	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	4 October 1995	Uiber, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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